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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/913,056	10/22/1997	NAKAYUKI YAMAMOTO	KP-8240	5317

466 7590 11/26/2002

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EXAMINER
WEBMAN, EDWARD J

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/913056	YAMANOUE
Examiner	**Group Art Unit**
WEBMAN	1617

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 1/10/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-27 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-27 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Prosecution is reopened in view of finding of new art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mazis et al in view of Roberts et al., Azria et al, Kissel et al, Japan 3-5427, EPA 215697, EPA 94157, Cooper, EPA 115627, Nakagawa et al, Masada et al, Hansen et al and Majeti.

Mazis et al teach transdermal delivery comprising a permeation enhancer, a vasodilator, and an active (abstract). One percent vasodilator and permeation enhancer are disclosed (column 3, lines 20, 44). The active is any transdermally deliverable drug, including proteinaceous drugs such as insulin (column 3, lines 30-33, column 4, line 15).

Roberts et al teach particular vasodilators such as nitroglycerin, prostaglandins and calcium antagonists (column 8, lines 5-9) to enhance topical delivery of a therapeutic agent.

Azria et al teach taurocholic acid as an absorption enhancer for calcitonin (abstract).

Kissell et al teach salts of fusidic acid as absorption enhancers for octreotide (title).

Japan 3-5427 teaches glycyrrhizic acid as an absorption enhancer for calcitonin (translated claim 1 supplied by applicant).

EPA 215697 teach acyl carnitines as absorption enhancers (abstract). Polypeptides are specified as actives (page 4 , lines 36-61).

EPA 94157 teaches cyclodextrin to increase absorption (abstract). Polypeptides are disclosed (page 3, line 13-page 6, line 2)

Cooper teaches acylazacycloheptane-ones as penetration enhancing agents (abstract). The enzyme asparaginase is disclosed as an active (column 20, line 18).

EPA 115627 teaches phosphatidyl choline and polyoxyethylated straight chain alcohols as absorbtion promoters for calcitonin (title, page 5, lines 5-7, 26, and page 6, line 3.

Nakagawa et al teach azacyloalkane derivatives as absorbtion promoters (abstract). Proteins such as insulin and calcitonin are specified (column 10, lines 21-26).

Masada et al teach fatty acids such as oleic acid as membrane-permeation promoters for motilin (abstract, column 2, line 59-column 3, line 6).

Hansen et al teach alkyl-2-pyrrolidones as penetration enhancers. (column 8 lines 5-6, 23). Peptides, including insulin, are disclosed (column 6, line 57).

It would have been obvious to one of ordinary skill to use nitroglycerin, prostaglandins and calcium agonists in the vehicle of Mazis et al to achieve the beneficial effect of vasodilators to enhance the delivery of a therapeutic agent in view of Roberts et al, to use taurocholic acid in the vehicle of Mazis et al to achieve the beneficial effect of an absorption enhancer for calcitonin in view of Azria et al, to use salts of fusidic acid in the vehicle of Mazis et al to achieve the

beneficial effect of absorption enhancers for octreotide in view of Kissel et al, to use glycyrrhizic acid in the vehicle of Mazis et al to achieve the beneficial effect of an absorption enhancer for calcitonin in view of Japan 3-5427, to use acyl carnitines in the vehicle of Mazis et al to achieve the beneficial effect of an absorption enhancer for peptides in view of EPA 215697, to use cyclodextrin in the vehicle of Mazis et al to achieve the beneficial effect of an absorption enhancer for polypeptides, to use acylazacycloheptane-ones in the vehicle of Mazis et al to achiever the beneficial effect of penetration enhancers for asparaginase in view of Cooper, to use phosphatidyl choline and polyoxyethylenated straight chain alcohols in the vehicle of Mazis et al to achieve the beneficial effect of absorption promoters for calcitonin, to use azacycloalkane derivatives in the vehicle of Mazis et al to achieve the beneficial effect of an absorption promoter for proteins such as insulin and calcitonin, to use oleic acid in the vehicle of Mazis et al to achieve the beneficial effect of a membrane permeation promoter for motilin in view of Masada et a, and to use alkyl-2-pyrrolidones in the vehicle of Mazis et al to achieve the beneficial effect of penetration enhancers for insulin in view of Hansen et al.

Applicants have argued that Mazis et al does not teach the claimed transmucosal delivery. The examiner has responded that Mazis et al teach saliva, indicative of delivery via mucosal tissue .Further, the examiner notes that Mazis et al also teach mucoid secretions, indicative of delivery via mucosal tissue. In applicants' reply brief, they point to column 5, lines 25-28, to show that Mazis et al teach that the disclosed bodily fluids such as saliva and mucoid secretions

"dissolve the water soluble gum that binds the MAZIS composition together." However, nowhere in the cited lines does the word "dissolve" appear. Mazis et al merely state that these fluids release the active from the vehicle. Applicants argue in their brief that the Mazis et al vehicle cannot be used in the mouth because the active will be ingested rather than absorbed. Such an argument is mere speculation. Even if, *arguendo*, Mazis et al do not disclose the claimed transmucosal delivery, that mode of delivery is merely an intended use. Intended uses are not considered patentable limitations in composition claims prosecuted before the USPTO

Applicants argue that Mazis et al teach irritant vasodilators. However, the examiner has pointed out that Mazis et al teach both irritant and non-irritant vasodilators (column 2, lines 62-63). Applicants argue in their brief that the vasodilators disclosed by Mazis et al are irritants that could not be used in rectal or nasal delivery. However, the examiner notes that applicants to do not claim such delivery. Further, the reference is not limited to exemplified vasodilators. Applicants also argue in their brief that the vasodilators disclosed by Mazis et al could not be used in a transmucosal vehicle because they are irritants. However, Majeti et al is cited for a transmuosal vehicle (abstract) containing menthol (column 6, line 8). It is further noted that Majeti et al is both a transdermal and a transmucosal vehicle (abstract), like Mazis et al. That is, a transdermal vehicle can also be used for transmucosal delivery.

Claims 1-3, 18, 19, 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyory et al in view of Sage, Jr. et al, and Haak et al.

Gyory et al teach iontophoretic delivery on a mucosal membrane (abstract). Sage, Jr. et al teach enhanced iontophoretic delivery of actives with a vasodilator (abstract). Proteins, including insulin and calcitonin are disclosed (column 6, line 6-16). Vasodilators, including nitroglycerin, are disclosed (column 7, line 32).

Haak et al teach the desirability of using a skin permeation inhancer, including alkyl polyethylene glycols, for iontophoretic delivery of an active (title, column 7, lines 3-12). Proteins such as insulin and calcitonin are specified (column 6, lines 36-68).

It would have been obvious to one of ordinary skill to add a vasodilator to the vehicle of Sage, Jr., et al to enhance the delivery of protein actives in view of Gyory et at and to add a skin permeation enhancer to the vehicle of Sage, Jr. et al to further do the same in view of Haak et al.

Claims 3-17, 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 3 "higher" is vague; it is subjective. What range of carbons? In claim 11, "polyoxyhethylene laurel" is indefinite. Is an ether or ester claimed? In claim 21, "usual" is vague; it also is subjective.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to E. Webman whose telephone number is 703-3-8-4432. The examiner can normally be reached on M-F from 9 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, S. Padmanabhan, can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

EDWARD J. WEBMAN
PRIMARY EXAMINER
GROUP 1500

SREENI PADMANABHAN
PRIMARY EXAMINER (SPE)
11/22/02